

44. (Amended) A transgenic mouse cell which comprises at least one endogenous altered LXR α allele that cannot express LXR α that responds to dietary cholesterol.

45. (Amended) The transgenic cell of claim 44, wherein said cell comprises two endogenous altered LXR α alleles that cannot express LXR α that responds to dietary cholesterol.

REMARKS

I. Status of the Claims

Claims 1, 2, 4-14, 21, 23-27, 29, 44 and 45 are pending in the application. Claims 1, 2, 4-14, 21, 23-27, 29, 44 and 45 stand rejected under 35 U.S.C. §112, first paragraph for lack of enablement. Claims 1, 2, 4-14, 21, 23-27, 29, 44 and 45 are rejected under 35 U.S.C. §112, second paragraph for indefiniteness. Claims 1, 2, 4-14, 21, 23-27, 29, 44 and 45 are rejected under 35 U.S.C. §102(a) over Peet *et al.* The specific grounds for rejection, and applicants' response thereto, are set out in detail below.

Applicants note that they previously submitted materials relating to this response on December 13, 2001. However, through an oversight, this response was not submitted at the same time. Thus, applicants request that this response be considered in conjunction with the materials previously submitted.

II. Objections

Claim 11 is objected to. A clarifying amendment is offered.

III. Rejections Under 35 U.S.C. §112

A. *Enablement*

Claims 1, 2, 4-14, 21, 23-27, 29, 44 and 45 are again rejected under the first paragraph of §112 on the grounds that the specification allegedly fails to provide enablement for the full scope thereof. In particular, the examiner argues that claims read on mutations outside LXR α . Applicants traverse, but in the interest of advancing the prosecution, have offered an amendment to all relevant claims stating that the endogenous LXR α gene is “altered,” in addition to being unable to respond to dietary cholesterol. It is believed that this amendment addresses the examiner’s concerns. Reconsideration and withdrawal of the rejection is, therefore, respectfully requested.

B. *Definiteness*

The examiner argues that the phrase “cannot express LXR α sufficient to provide the capacity to respond to dietary cholesterol.” Applicants traverse.

The examiner actually parses out two different issues with respect to the above-quoted phrase. First, it is stated that the specification does not identify the **amount** of dietary cholesterol involved. The examiner has misunderstood the phrase. As stated at page 58, line 27 of the specification, dietary cholesterol simply refers to that cholesterol provided from exogenous (*i.e.*, diet) sources, as opposed to that cholesterol that is synthesized in the organism (endogenous). Thus, there is no indefiniteness associated with this term as it is used, and the entire discussion of relative amounts (normal, low or high levels) is irrelevant. Rather, the claim simply states that the endogenous altered LXR α cannot respond to **any** dietary cholesterol, *i.e.*, cholesterol above and beyond that produced endogenously.

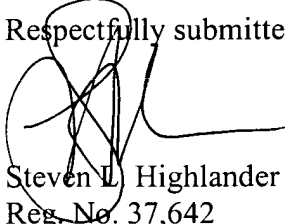
Second, the examiner asks "what specific response or what level of response is contemplated," and "what capacity is being measured." As discussed in the specification, LXR α assists in the clearing and metabolism of cholesterol; in the absence of this function, animals show dramatic hepatic cholesterol accumulation. Again, there is no "level" issue – the alteration in the endogenous LXR α eliminates its ability to metabolize cholesterol. Thus, the claims simply reflect the loss of normal LXR α function due to the alteration. However, in order to clarify the claims, applicants have provided an amendment such that the terms "sufficient" and "capacity" are no longer recited.

Thus, applicants respectfully submit that the pending claims are not indefinite, and are even more clear in their amended form as presented herein. Reconsideration and withdrawal of the rejection is, therefore, respectfully requested.

IV. Conclusion

In light of the foregoing, applicants respectfully submit that all claims are in condition for allowance, and an early indication to that effect is earnestly solicited. Should Examiner Woitach have any questions regarding this response, he is invited to contact the undersigned at the telephone number listed below.

Respectfully submitted,



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APPENDIX A - MARKED UP COPY OF CLAIMS

1. (Amended) A transgenic mouse, the cells of which comprise at least one endogenous altered LXR α allele that cannot express LXR α [sufficient to provide the capacity to respond] that responds to dietary cholesterol.
2. (Amended) The transgenic mouse of claim 1, wherein said cells comprise two endogenous altered LXR α alleles that cannot express LXR α [sufficient to provide the capacity to respond] that responds to dietary cholesterol.
4. (Amended) The transgenic mouse of claim 1, wherein a transcript produced from said endogenous altered LXR α allele contains an interruption in the LXR α coding sequence.
5. (Amended) The transgenic mouse of claim 2, wherein a transcript produced from said endogenous altered LXR α alleles both contain an interruption in the LXR α coding sequences.
6. (Amended) The transgenic mouse of claim 1, wherein said endogenous altered LXR α allele contains a nonsense mutation that truncates the corresponding encoded LXR α polypeptide.
7. (Amended) The transgenic mouse of claim 2, wherein said endogenous altered LXR α alleles both contain a nonsense mutation that truncates the corresponding encoded LXR α polypeptide.
8. (Amended) The transgenic mouse of claim 1, wherein said endogenous altered LXR α allele contains a deletion of LXR α coding sequences.
9. (Amended) The transgenic mouse of claim 2, wherein said endogenous altered LXR α alleles both contain a deletion of LXR α coding sequences.

10. (Amended) The transgenic mouse of claim 1, wherein said endogenous altered LXR α allele contains a mutation in the 5' regulatory region of the LXR α gene.

11. (Amended) The transgenic mouse of claim 2, wherein said altered endogenous LXR α alleles both contain a mutation in the 5' regulatory region of the [LXR α s] LXR α genes.

21. (Amended) A method for screening a candidate substance for the ability to reduce cholesterol levels in a mammal comprising:

- (a) providing a transgenic mouse, the cells of which comprise at least one endogenous altered LXR α allele that cannot express LXR α [sufficient to provide the capacity to respond] that responds to dietary cholesterol;
- (b) treating said mouse with said candidate substance; and
- (c) monitoring a cholesterol-related phenotype in said mouse,

wherein a reduction in said cholesterol-related phenotype in said mouse treated with said candidate substance, as compared to a similar mouse not treated with said candidate substance, indicates that said candidate substance reduces cholesterol levels.

26. (Amended) The method of claim 21, wherein said cells comprise two endogenous altered LXR α alleles that cannot express LXR α [sufficient to provide the capacity to respond] that responds to dietary cholesterol.

27. (Amended) A method for screening a candidate substance for the ability to increase bile acid synthesis in a mammal comprising:

- (a) providing a transgenic mouse, the cells of which comprise at least one endogenous altered LXR α allele that cannot express LXR α [sufficient to provide the capacity to respond] that responds to dietary cholesterol;
- (b) treating said mouse with said candidate substance; and

- (c) monitoring a bile acid-related phenotype in said mouse,
- wherein an increase in said bile acid-related phenotype in said mouse treated with said candidate substance, as compared to a similar mouse not treated with said candidate substance, indicates that said candidate substance increases bile acid synthesis.
44. (Amended) A transgenic mouse cell which comprises at least one endogenous altered LXR α allele that cannot express LXR α [sufficient to provide the capacity to respond] that responds to dietary cholesterol.
45. (Amended) The transgenic cell of claim 44, wherein said cell comprises two endogenous altered LXR α alleles that cannot express LXR α [sufficient to provide the capacity to respond] that responds to dietary cholesterol.